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Letter to the Editor

Genotype and Phenotype in Angelman Syndrome Caused by Paternal UPD 15

To the Editor:

Angelman syndrome (AS) is caused by a number of different genetic anomalies [Williams et al., 1995], including de novo deletion of the maternal chromosome 15 (70% of cases), paternal uniparental disomy 15 (UPD) (3–4%), and "imprinting mutations" (3–4%). Approximately 20% of patients with clinical findings of AS show normal results of all currently available diagnostic tests, including FISH analysis, methylation analysis, and UPD analysis using polymorphic DNA markers. In this group, AS may be familial and is linked to 15q11-q13 loci [Wagstaff et al., 1992].

Several investigators have described the phenotype in patients with AS caused by UPD as milder than that in deletion AS [Freeman et al., 1993; Bottani et al, 1994; Gillessen-Kaesbach et al., 1995]. In a recent review of AS, Williams et al. [1995] stated that "Patients with AS resulting from UPD seem to have less ataxia, fewer or no seizures, better physical growth, and relatively higher cognitive skills than do patients with large deletions."

The question of phenotypic severity in AS in relation to genotypic class is not only of importance in understanding the pathogenesis of AS but may be of practical significance in cases where AS is diagnosed prenatally. AS deletions are seldom detected by routine prenatal chromosome analysis. On the other hand, paternal UPD 15 is associated with isochromosomes or translocations involving chromosome 15 in a significant fraction of cases [Smeets et al., 1992; Freeman et al., 1993; Smith et al., 1994; Zackai et al., 1995], and recently an ASHG/ACMG committee [1996] recommended prenatal testing for UPD in cases where these rearrangements involving chromosome 15 are detected by amniocentesis or CVS.

Recently we evaluated a 10-year-old girl with severe developmental delay and seizures (Fig. 1). She was born to a 14-year-old primigravid mother and 22-year-old father, both of Hispanic origin, at 38 weeks of gestation after an uncomplicated pregnancy. There was significant motor delay, and she did not begin to walk without support until after age 6 years. She has no speech and very little evidence of language comprehension. She developed seizures at 5 years which have been difficult to control despite a variety of different medications. She underwent inguinal hernia repair at 3 years and tonsillectomy and adenoidectomy because of obstructive sleep apnea at 9 years. Family history was notable for bilateral inguinal hernias in the mother, repaired at 5 years, and childhood seizures in the mother that resolved at 6 years. On examination, the patient's weight was at the 90th centile, height at the 75–90th centile, and head circumference at the 50th centile. She had a short attention span and increased motor activity, with intermittent alternating exotropia, prominent jaw, and widely-spaced teeth. Muscle tone and strength were normal; movements were jerky and gait was markedly ataxic.

Karyotype analysis and FISH analysis with D15S11 and GABRB3 probes (Oncor, Gaithersburg, MD) were normal, but methylation analysis of D15S63 showed a paternal-only pattern. Polymorphism analysis by PCR for 7 chromosome 15 simple tandem repeat loci (ACTC, D15S642, D15S643, D15S652, D15S657, D15S659, and D15S817) showed the mother to be heterozygous at all seven loci; for each of these loci, the AS child was homozygous for an allele not present in the mother. Paternal blood was not available for analysis.

The phenotype of this child is, in our experience, not substantially different from the average severity in deletion AS, and we have seen several patients with typical AS deletions who were phenotypically milder than this child. In addition to the reports cited above suggesting a milder phenotype in AS caused by UPD, 3 other reports, including those of Malcolm et al. [1991], Nicholls et al. [1992], and Smith et al. [1994] have not described the phenotype in UPD AS as atypical or mild. The factors that may account for the phenotypic variability in UPD AS are unknown; they may include unlinked modifier genes, low-level mosaicism for chromosome 15 monosomy or trisomy, and homozygosity for chromosome 15 mutations in cases of isodisomy. Bottani et al. [1994] hypothesized that the milder phenotype that they observed might be caused by "leaky expression of the 'AS gene' from the paternal allele"; if this explanation is correct, then the degree of leakiness may be variable for different paternal alleles. Identification of the AS gene will make it possible to test this hypothesis.

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Fig. 1. Frontal view of patient.

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